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(54) Title: CROSS-LINKED AMYLOSE AS A BINDER/DISINTEGRANT IN TABLETS (57) Abstract <p>The present invention is concerned with the manufacture of solid dosage units (pharmaceutical and others). More specifically, the invention is related to powders of cross-linked amylose, having a specific cross-linking degree for use as tablet binders and disintegrants.</p>		

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CROSS-LINKED AMYLOSE AS A BINDER/DISINTEGRANT IN TABLETS

FIELD OF THE INVENTION

5 The present invention is related to powders of cross-linked amylose, having a specific cross-linking degree for use as a tablet binder and/or disintegrant, the tablets being prepared by direct compression.

BACKGROUND OF THE INVENTION

10 In the pharmaceutical industry, tablets appear to be the most advantageous form for the administration of a drug. Packaging and handling are normal operations onto which pharmaceutical products are submitted, which makes tablets the preferred choice. Additionally, tablets are frequently employed in non
15 pharmaceutical fields such as fish foods, plant growth regulators, pesticides, herbicides and the like.

 These tablets must show good mechanical qualities in view of the manufacturing process involved and the subsequent handling and packaging. The
20 most important mechanical properties are the hardness and the resistance to friability. These features are closely related to one another since an increase in tablet hardness generally leads to a decrease in tablet friability. The term hardness describes the resistance of the tablet to stresses and strains of transportation and storage. Usually, one measures the crushing-strength defined as "that compressional
25 force which, when applied diametrically to a tablet, just fractures it" (Brook et al. *J. Pharm. Sci.*, 1968, 57, 481-484). If the hardness of the tablet is insufficient i.e. when the crushing-strength value is too low, tablets are likely to break, especially during handling when they are subjected to repeated shocks. Furthermore, excessive friability may cause dusting and crumbling of the tablet, resulting in a diminution in
30 active ingredient dosage and in a poor appearance of the tablet.

Thus, the manufacture of tablets involves the optimization of these two characteristics. If a quick release of the drug is desired, then the tablet must also possess acceptable disintegration characteristics both *in vivo* and *in vitro*.

5 The simplest and most economical procedure for the manufacturing of tablets is the direct compression of all the ingredients distributed homogeneously. The procedure i.e. the powder compression in a tablet puncher follows directly the dry blending of one or more active ingredients and at least one of the following: filler, binder, disintegrant and lubricant, and the like.

10 Materials such as sodium chloride, saccharose, salicylamide, hexamethylenetetramine and the like are readily directly compressed alone in dry form into a coherent and compact mass in a conventional tablet puncher. However, the majority of active ingredients require a binding agent to maintain the drug
15 particles together in a tablet. Such binding agent increases the strength of the compressed tablet and decreases its friability, leading to an improvement in the tablet appearance and mechanical characteristics. An appropriate binding agent possesses flowing properties, can be blended easily and is inert and non-toxic. Conventional binders currently in use include: microcrystalline cellulose (Avicel PH-
20 101™ and PH-102™) polyvinylpyrrolidone (Kollidon™, Plasdone™), cornstarch, wheat starch, potato starch, modified starches, gums, and the like. All these products are usually employed in direct compression at a minimum concentration level of 20%.

25 Disintegration rate is important when the tablet is contacted with fluids such as body fluids. Tablets should immediately fall apart into distinct particles whenever the drug is to be released very quickly. They must disintegrate rapidly enough to provide adequate blood levels of drug.

30 If quick disintegration of the tablet is required, disintegrants are added. A effective disintegrant is an agent that promotes destruction of the tablet physical integrity. Typical disintegrants are: corn starch, gelatinized starches (Sta Rx™), modified starches e.g. sodium starch glycolate (Primojel™).

Co-pending application U.S.S.N. 787,721 filed October 31, 1991 discloses cross-linked amylose having a cross-linking degree of 1 to 10, which possesses controlled release properties when mixed with a pharmaceutical product. However, such controlled release properties are observed only if the amount of cross-linked amylose is above 40% by weight in the tablet.

Short et al. (US 3,622,677) discloses a binder/disintegrant constituted of modified and/or cross-linked starch. However, the binding properties of their materials are considerably low, which means that a significant amount of the binder needs to be present in the tablet.

Trubiano (US 4,369,308) describes modified starches for use as disintegrant. These starches however have poor binding properties.

Some materials, for example microcrystalline cellulose (Avicel PH 101™ and Avicel PH 102™) present binding and disintegrating characteristics of both binders and disintegrants. Despite the existence of many binders and disintegrants, pharmaceutical researchers have continued their efforts to develop improved materials capable of being employed as a binder and/or as a disintegrant in the preparation of tablets by direct compression.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is now provided an improved binder for the manufacture of tablets. The binder of the present invention also acts as a disintegrant. More specifically, the binder of the present invention consists in cross-linked amylose having a cross-linking degree of from 6 to 30. The binder can be used in the manufacture of tablets by conventional techniques such as direct compression.

Tablets comprising the above binder also fall within the scope of the present invention, and may be chewable tablets. The concentration of cross-linked amylose in the tablet must be lower than 35% by weight.

IN THE DRAWINGS

Figure 1 illustrates hardness versus compression strength for tablets containing 5% of cross-linked amylose;

5 Figure 2 illustrates hardness versus compression strength for tablets containing 15% of cross-linked amylose;

Figure 3 illustrates hardness versus compression strength for tablets containing 20% of cross-linked amylose;

Figure 4 illustrates hardness versus compression strength for tablets containing 25% of cross-linked amylose;

10 Figure 5 illustrates the hardness versus the cross-linking degree when tablets are compressed at 8 tons/cm²;

Figure 6 illustrates the hardness versus the compression strength for tablets containing 20% by weight of Avicel or CLA-15 as the binder; and

15 Figure 7 illustrates the hardness versus the compression strength for tablets containing 25% by weight of Avicel or CLA-15 as the binder.

DETAILED DESCRIPTION OF THE INVENTION

20 The cross-linking of amylose is well known in the literature. For example, it can be carried out by reacting amylose with epichlorohydrin in an alkaline medium. Several cross-linking agents are available to cross-link amylose, such as 2,3-dibromopropanol, epichlorohydrin, epichlorohydrin being more preferred. Most preferred cross-linked amylose include those obtained by cross-linking 6 to 30 g of epichlorohydrin per 100 g of amylose, corresponding to a cross-linking degree
25 of 6 to 30.

Surprisingly, it has been discovered that the above cross-linked amylose can be dry mixed in an amount not exceeding 35% by weight with active ingredients and optionally conventional tablet excipients, such as fillers, lubricants,
30 and the like, to prepare formulations which are directly compressible into tablets in conventional tablet punchers.

To illustrate the present invention, tablets containing cross-linked amylose of various cross-linking degrees, α -monohydrate lactose 100 mesh and magnesium stearate were prepared. The crushing strength, the friability and the disintegration times of the tablets were investigated. The results showed excellent
5 binding and disintegrating properties for cross-linked amylose having a cross-linking degree from 6 to 30. The influence of the compressional force, the cross-linking degree and the concentration of cross-linked amylose were also carefully examined.

Cross-linked amylose

10

Amylose is a natural substance obtained from starch, a binary compound constituted by amylose non-ramified polyglucose chain wherein the repetitive glucose units are linked by α -1,4-glucosidic bonds, and by the amylopectin branched polyglucose polymer, which contains many branching points based on α -1,6-
15 glucosidic bonds.

The cross-linking of amylose is well-known in the literature. For example, the desired cross-linking can be carried out in the manner described by Mateescu et al. in *Analytical Letters*, 1985, 18, 79-91, by reacting amylose with
20 epichlorohydrin in an alkaline medium.

Essentially, the amylose is swollen in an alkaline medium such as sodium hydroxide at 55°C. After complete homogenization, an appropriate amount of cross-linking agent is added and homogenization continues for 45 min. The
25 duration of heating can be varied as well as the amount of cross-linking agent used in the reaction. The cross-linked amylose gel is then neutralized with acetic acid, washed with water/acetone and dried with pure acetone. Finally, the polymer powder is exposed to air for 3 hours and stored in hermetic glass bottles.

30

The binding properties of these cross-linked amylose are comparable or even superior in some instances, to microcrystalline cellulose (Avicel PH-102™) which is widely used in the field. Certain cross-linked amylose advantageously

present also excellent disintegration properties, thus preventing the need of an additional excipient having these properties in the tablet.

5 It should be noted that the unexpected and highly effective binding properties of cross-linked amylose have not been observed with cross-linked starch or cross-linked amylopectin. This phenomenon is essentially due to the fact that amylose is constituted of linear non-ramified chains of polyglucose susceptible to be associated by hydrogen bonds. On the other hand, the presence of branched chains in amylopectin does not allow molecular rearrangements, responsible for the binding
10 properties. Since starch contains over 75% by weight of amylopectin, it is normal that it is not as effective as amylose. Thus, the use of cross-linked amylose constitutes definitively an improvement when compared to starch.

Preparation of tablets

15 The binding properties of cross-linked amylose and disintegrating properties of tablets containing same were studied. The tablets also contained α -monohydrate lactose 100 mesh as the filler and magnesium stearate as the lubricant. These latter two products are used on a current basis in the pharmaceutical industry. Furthermore, it is well-known that α -monohydrate lactose presents poor binding and
20 disintegrating properties (Bolhuis, *Pharm. Weekblad*, 1973, 108, 469-481). Magnesium stearate is also recognized to decrease crushing-strength of lactose tablets and to increase disintegration times by hindering the water penetration into the tablet (Lerk et al., *Pharm. Acta Helv.*, 1977, 52(3), 33-39). The poor binding and disintegrating properties of the lubricant and filler used further illustrate the
25 unexpected binding and disintegrating properties of cross-linked amylose having a cross-linking degree of 6 to 30.

Typically, α -monohydrate lactose 100 mesh and cross-linked amylose were mixed in a Turbula shaking mixer for 3 minutes. Magnesium stearate was
30 subsequently incorporated, and the mixture further agitated for an additional 2 minutes.

Tablets weighing about 400 mg each were obtained by direct compression in a hydraulic press at 2, 4, 6 and 8 tons/cm². The tablets were of 1.26 cm diameter and thickness of about 2.0 to about 2.2 mm.

5 Determination of the tablet crushing-strength

The crushing-strength (Lerk, 1977) has been determined by using a tablet hardness tester (Strong Kobb Arner, model B124). The value is expressed in kg and is the mean of five measurements.

10 Determination of the tablet friability

The index of friability is determined by using a friabilitor (Pharma Test, Type PTFR II, Hainburg, Germany). 13 tablets are shaken in the apparatus for 4 min (25 rpm). The friability index is calculated according to the following equation:

$$l = (1 - M_b/M_a) \times 100$$

wherein M_a = weight of the tablet before shaking;
 M_b = weight of the tablet after the shaking.

Determination of the tablet disintegration time

20 Disintegration times were determined according to method <701> for uncoated tablets of USP XX using 1 litre of water at 37°C as the medium. The disintegration time reported is the mean of three measurements.

25 The following examples are provided to illustrate the invention rather than limit its scope. Other variations within the scope of the present invention will be easily appreciated by the skilled workman.

Example 1

30 Cross-linked amylose synthesis (CLA-6): 1 kg of corn amylose (Sigma Chemicals, St.Louis) and 6 L of sodium hydroxide 1N (55°C) are mixed in a Hobart A200-T planetary mixer. After 15 minutes of homogenization, a volume of 50.8 ml (60 g, $d = 1.18$ g/ml) of epichlorohydrin is added slowly and homogenization continues for another 45 min. The CLA gel is then neutralized with acetic acid and

washed three times through a Büchner funnel with a solution of water:acetone 60:40. The last step consists of washing and drying the resulting solid gel with pure acetone directly on a Büchner filter. Finally, the polymer is exposed to air for 3 hours and stored in hermetic glass bottles. The granulometric fraction between 50 and 250
5 microns was selected in all the experiments.

This polymer will be referred to as CLA-6.

Other CLA polymers are obtained under strictly identical conditions
10 but changing the amount of epichlorohydrin to 110, 150 and 300 g to obtain CLA-11, CLA-15 and CLA-30. In the figures, CLA-0 indicates that native amylose was treated in the same manner as above, except that no epichlorohydrin was added.

Example 2

15 α -monohydrate lactose 100 mesh and cross-linked amylose prepared in Example 1 were mixed in a Turbula shaking mixer for 3 minutes; magnesium stearate was added, and the mixture further agitated for 2 minutes.

The proportions of the various ingredients in the tablets are reported
20 in Table 1. Avicel PH-102™ was used as a comparison since it is one of the better binding/disintegrating agent presently available on the market.

TABLE 1

25

Concentration of each ingredient in the tablets			
<u>Mixture</u> (number)	<u>Lactose</u> (%)	<u>Mg stearate</u> (%)	<u>CLA content</u> (%)
1	99.8	0.2	0.0
30 2	94.8	0.2	5.0
3	84.8	0.2	15.0
4	79.8	0.2	20.0
5	74.8	0.2	25.0

35 Tablets weighing about 400 mg each were obtained by direct compression in a hydraulic press at 2, 4, 6 and 8 tons/cm². The tablets were of 1.26 cm diameter and thickness of about 2.0 to about 2.2 mm.

Example 3

The crushing-strength results are presented in Figures 1, 2, 3 and 4. The crushing-strength (kg) is plotted against the compressional force (t/cm^2) for the different CLA-n prepared in example 1. The plot of the crushing-strength versus the compression force of lactose tablets deprived of binder are also reported in Figures 1, 2, 3 and 4 to assess clearly the effect of the compression force and the presence of the binding agent on the crushing-strength.

It can be seen in Figure 1 that tablets made of lactose and magnesium stearate without any binder are not very hard and break easily (all the crushing-strength values are below 8.4 kg, which is the best value obtained). Furthermore, an increase in compression force to 8 tons/ cm^2 causes a dramatic decrease in hardness (2.7 kg). This is caused by the lactose particles which tend to break down in smaller particles when high compressional forces are applied.

The effect of cross-linked amylose is clearly demonstrated in Figures 1 to 4 since their presence in the tablets leads generally to an increase in hardness. The beneficial effect is particularly evident when the concentration of cross-linked amylose is equal or higher than 15%. Thus, the cross-linked amylose concentration is an important parameter for obtaining satisfactory tablet hardness.

Another important point is the effect of the cross-linking degree on the tablet hardness for identical concentrations of cross-linked amylose (Figures 1 to 4). It can be seen that CLA-0 has almost no effect on the tablet hardness, except at a compression force of 8 tons/ cm^2 when the polymer concentration is equal or higher than 15%. It is also apparent that the best results are obtained with a cross-linking degree of 15 (CLA-15). The crushing-strength has been plotted against the cross-linking degree for different concentrations of polymer, in the case of a compressional force equal to 8 tons/ cm^2 to show more clearly the effect of cross-linking degree on the tablet hardness (Figure 5). In any event, cross-linked amylose having a cross-linking degree ranging from about 6 to about 30 improved the hardness of the tablet when compared to those containing lactose and magnesium

stearate and deprived of binder. Thus, the cross-linking degree of cross-linked amylose is a critical parameter in the obtention of an adequate tablet hardness.

5 Finally, tablets containing CLA-15 were compared to tablets containing Avicel PH-102™ and tablets deprived of binder (Figures 6 and 7). There is clearly an improvement in the binding properties when 20% or 25% of binder are used (Avicel PH-102™ or CLA-15). Furthermore CLA-15 presented much better binding properties than Avicel PH-102™, demonstrating the utility of cross-linked amylose in the preparation of tablets by direct compression.

10

Example 4

Friability results are presented in Table 2. Clearly, cross-linked amylose shows excellent binding properties leading to very low values of friability. It is particularly evident that CLA-15 again demonstrated superior binding properties when compared to other CLAs and Avicel PH-102™. The influence of the cross-linked amylose concentration is also evident, a higher binder concentration leading to a lower friability of the tablet. These results are in perfect agreement with the results obtained for hardness experiments (see Example 3).

15

TABLE 2
Friability of tablets

Binder 5%	Compression force (tons/cm ²)			
	2	4	6	8
CLA-0	*	1.09	*	*
CLA-6	*	0.72	*	*
CLA-11	1.28	0.94	0.75	1.05
CLA-15	1.31	0.65	0.6	0.7
CLA-30	1.44	0.85	0.81	*
Avicel PH 102	1.33	0.64	0.67	*

Binder 15%	Compression force (tons/cm ²)			
	2	4	6	8
CLA-0	*	1.35	1.18	1.19
CLA-6	0.71	0.46	0.33	0.40
CLA-11	0.80	0.48	0.37	0.37
CLA-15	0.68	0.29	0.28	0.27
CLA-30	1.03	0.49	0.55	0.30
Avicel PH 102	1.78	0.42	0.33	0.33

Binder 20%	Compression force (tons/cm ²)			
	2	4	6	8
CLA-0	*	1.27	1.27	1.19
CLA-6	0.39	0.36	0.34	0.30
CLA-11	0.63	0.43	0.34	0.34
CLA-15	0.50	0.27	0.18	0.20
CLA-30	0.82	0.41	0.40	0.34
Avicel PH 102	0.69	0.34	0.31	0.29

Binder 25%	Compression force (tons/cm ²)			
	2	4	6	8
CLA-0	*	1.44	1.25	1.29
CLA-6	0.54	0.40	0.31	0.22
CLA-11	0.53	0.28	0.25	0.23
CLA-15	0.30	0.16	0.15	0.12
CLA-30	0.62	0.35	0.30	0.29
Avicel PH 102	0.57	0.31	0.23	0.22

* Tablets broke during experiment

Example 5

Disintegration results proved to be excellent as well for cross-linked amylose CLA-15 and CLA-30 as for Avicel PH-102™ when they are used at a concentration of 20% in the tablet. All the disintegration times were between 30 and 90 seconds for compressional forces ranging from 2 to 8 tons/cm². Mixtures of various percentages of cross-linked amylose of different cross-linking degrees were studied in regard of the disintegration times and presented similar results, that is, the disintegration times varied from 30 to 90 seconds. The cross-linked amylose used for the purposes of the present invention possesses binding properties combined with disintegrating properties as long as it is employed in accordance with the restrictions specified above.

Example 6

CLA-8 and Cross-Linked Amylopectine-8 were synthesized in the same manner as in Example 1. Tablets containing 20% of CLA-8 and 20% of cross-linked amylopectine-8 were prepared at a compressional force of 8 tons/cm², in conditions identical to those indicated in Example 2. The crushing-strength values are reported in Table 3.

TABLE 3

Crushing-strength values of CLA-8, Cross-Linked Amylopectine-8 and lactose 100 mesh.

CLA-8 (20%)	Cross-Linked Amylopectine-8	Lactose 100 mesh
14.5	7.5	2.0
13.5	8.0	3.0
15.0	8.5	3.0
13.0	8.5	2.0
13.5	8.5	3.5
mean = 13.9	mean = 8.2	mean = 2.7

Table 3 clearly illustrates that CLA binding properties are largely superior to those of cross-linked amylopectine. The beneficial effect of CLA is better even with a cross-linking degree as low as 8. Starch being largely composed of amylopectine, it becomes obvious that the use of CLA constitutes an improvement when compared to starch and that the role of amylose is of major importance, probably due to its regular non branched structure, susceptible of being stabilized by hydrogen bonds.

It is evident that the skilled workman will be able to select properly the cross-linking degree and the concentration of cross-linked amylose to formulate adequately tablets to be prepared by direct compression, these tablet being hard, non friable and readily disintegrative when placed in aqueous medium.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains, and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

CLAIMS

1. A tablet obtained by direct compression of a mixture
5 comprising an active ingredient and a binder/disintegrant, characterized in that:

said binder/disintegrant is a cross-linked amylose wherein the cross-linking has been carried out with from about 6 to about 30 grams of cross-linking agent per 100 grams of amylose, and

said cross-linked amylose is present in the tablet in an amount not
10 exceeding 35% by weight.

2. A tablet according to claim 1, wherein the cross-linked amylose is present in the tablet in an amount ranging from 5% to 25% by weight.

15 3. A tablet according to claim 2, wherein the cross-linked amylose is present in the tablet in an amount ranging from 10% to 20% by weight.

4. A tablet according to any one of claims 1 to 3 further comprising at least one additional excipient.

20 5. A tablet according to claim 4, wherein said additional excipient is selected from the group consisting of fillers and lubricants.

25 6. A tablet according to any one of claims 1 to 5, wherein said cross-linking agent is epichlorohydrin.

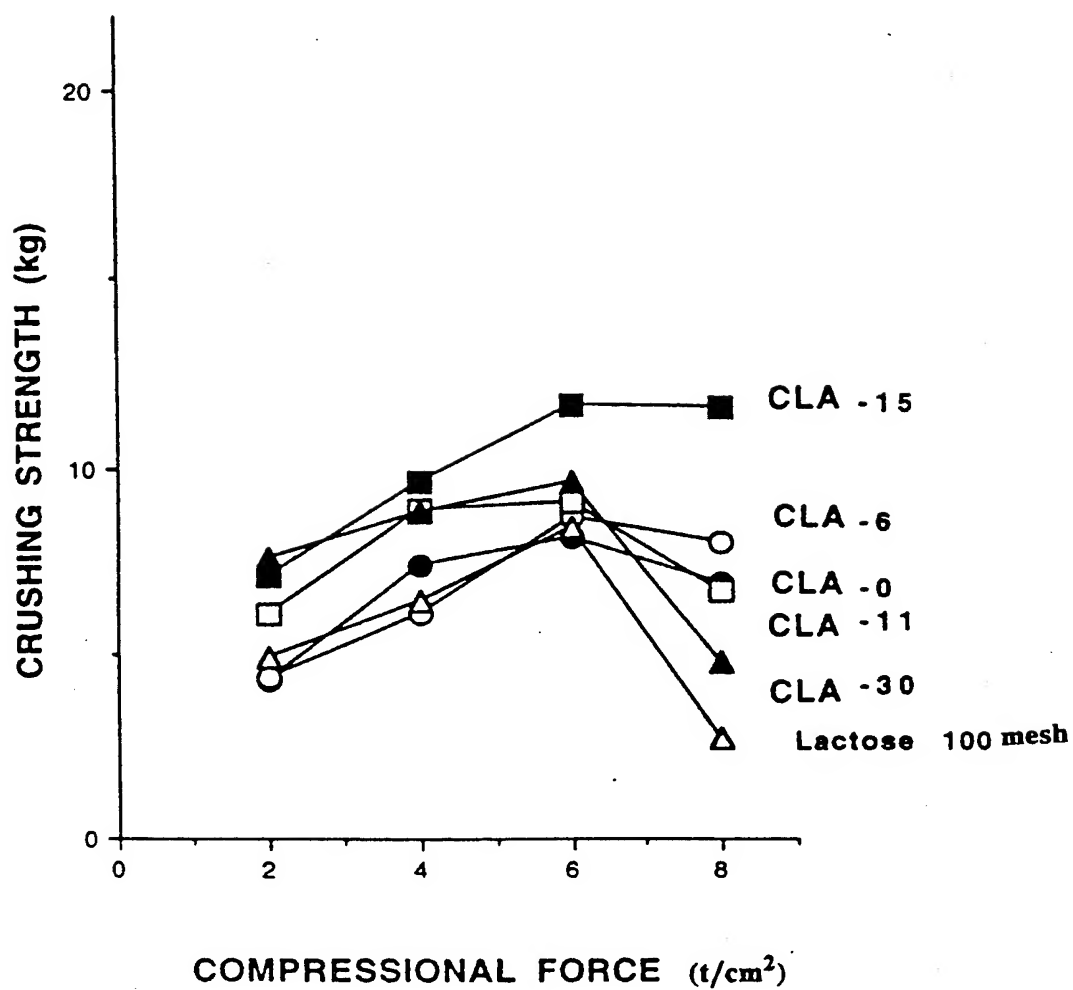
7. A tablet according to any one of claims 1 to 6, wherein said active ingredient is a drug.

30 8. A tablet according to any one of claims 1 to 7, which is in the form of a chewable tablet.

9. A tablet according to any one of claims 1 to 8 which is disintegrant within 90 seconds in water at 37°C.

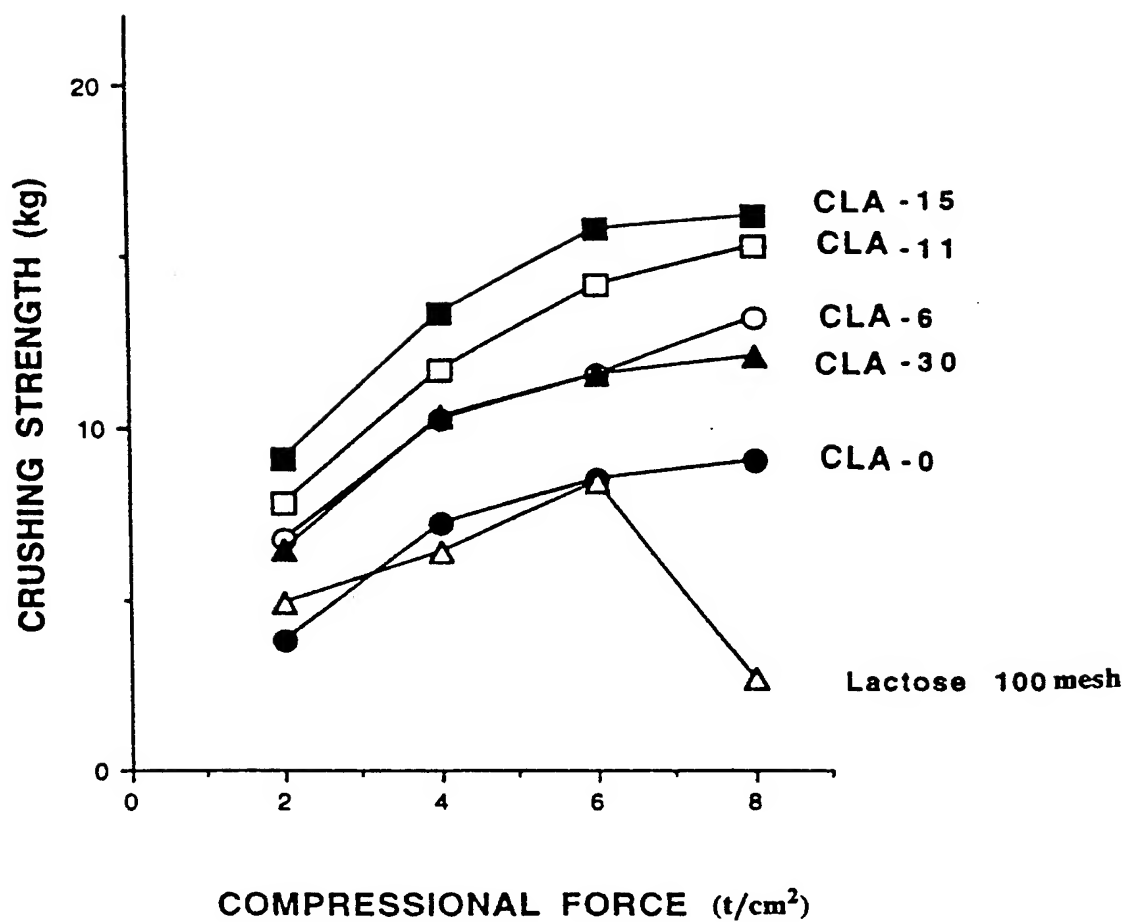
10. A tablet according to any one of claims 1 to 9 wherein the
5 cross-linked amylose has been cross-linked with about 15 grams of cross-linking agent per 100 grams of amylose.

1 / 7



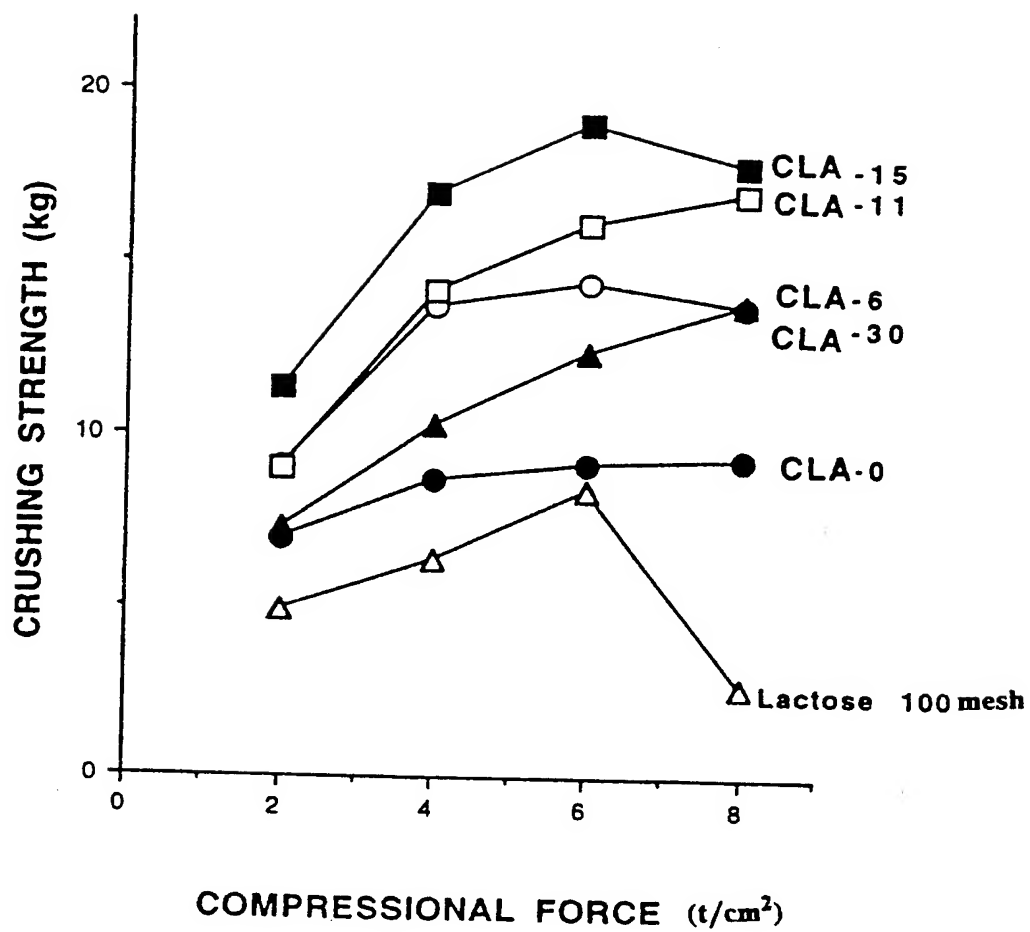
**FIGURE 1 . CRUSHING STRENGTH vs COMPRESSIONAL FORCE
(TABLETS CONTAINING 5% OF CROSS-LINKED AMYLOSE).**

2 / 7



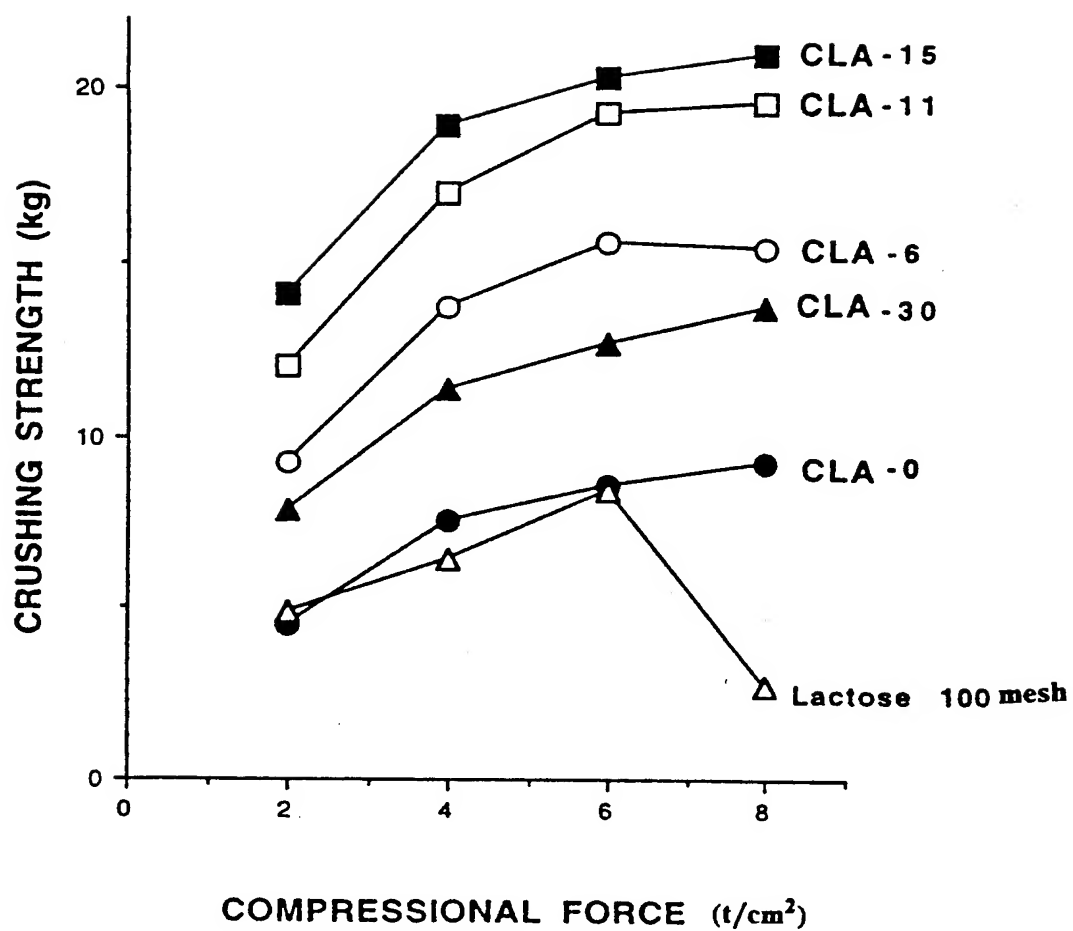
**FIGURE 2 . CRUSHING STRENGTH vs COMPRESSIONAL FORCE
(TABLETS CONTAINING 15% OF CROSS-LINKED AMYLOSE).**

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**FIGURE 3 . CRUSHING STRENGTH vs COMPRESSIONAL FORCE
(TABLETS CONTAINING 20% OF CROSS-LINKED AMYLOSE).**

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**FIGURE 4 . CRUSHING STRENGTH vs COMPRESSIONAL FORCE
(TABLETS CONTAINING 25% OF CROSS-LINKED AMYLOSE).**

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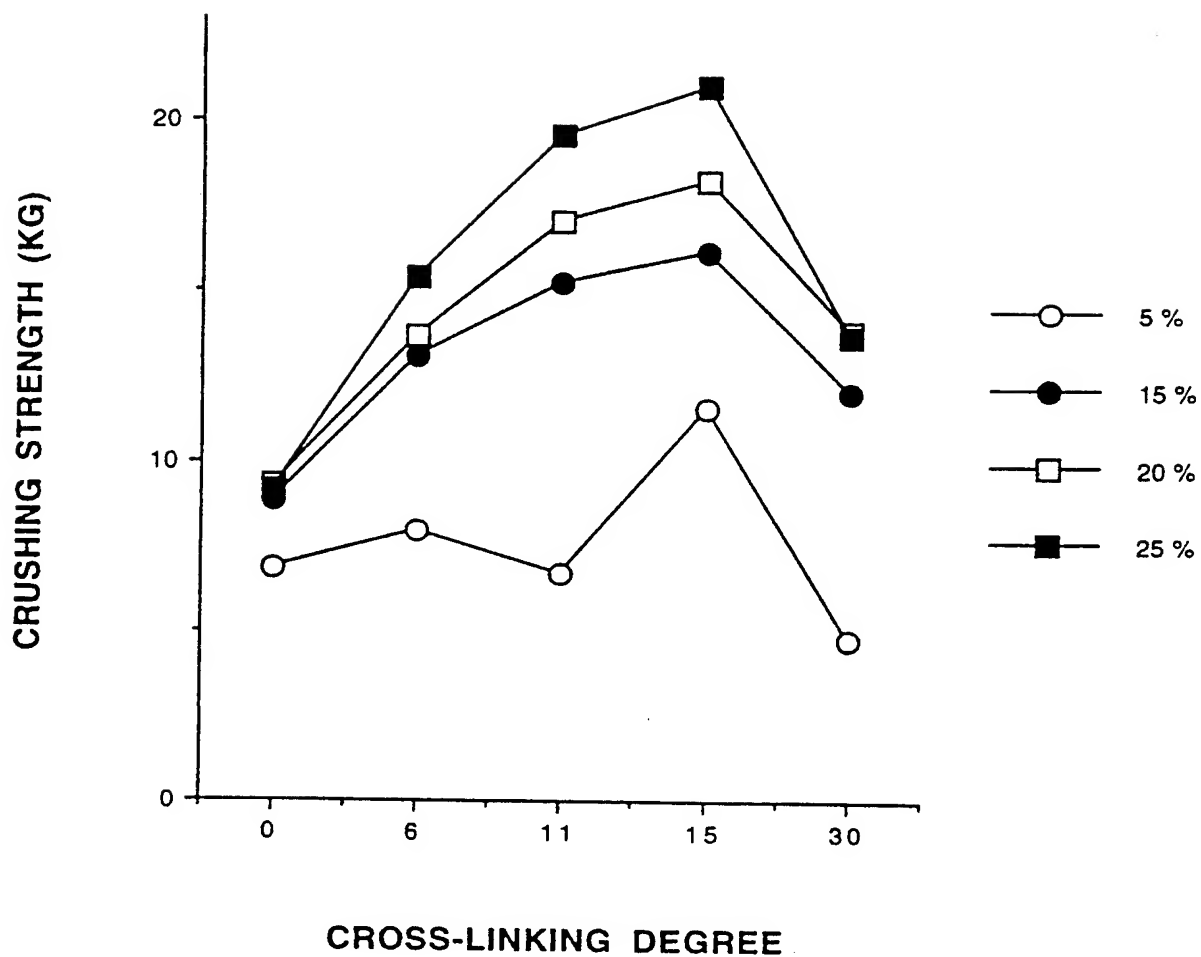
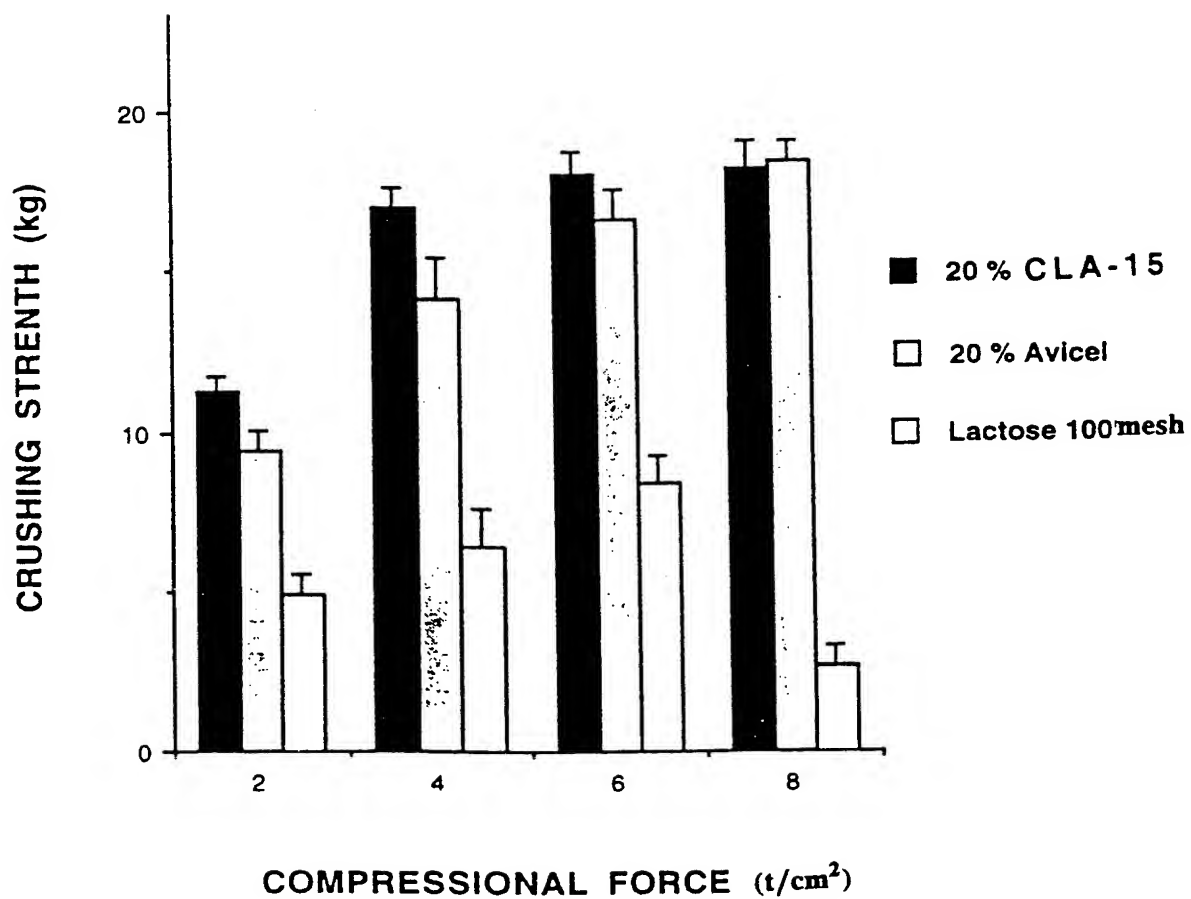


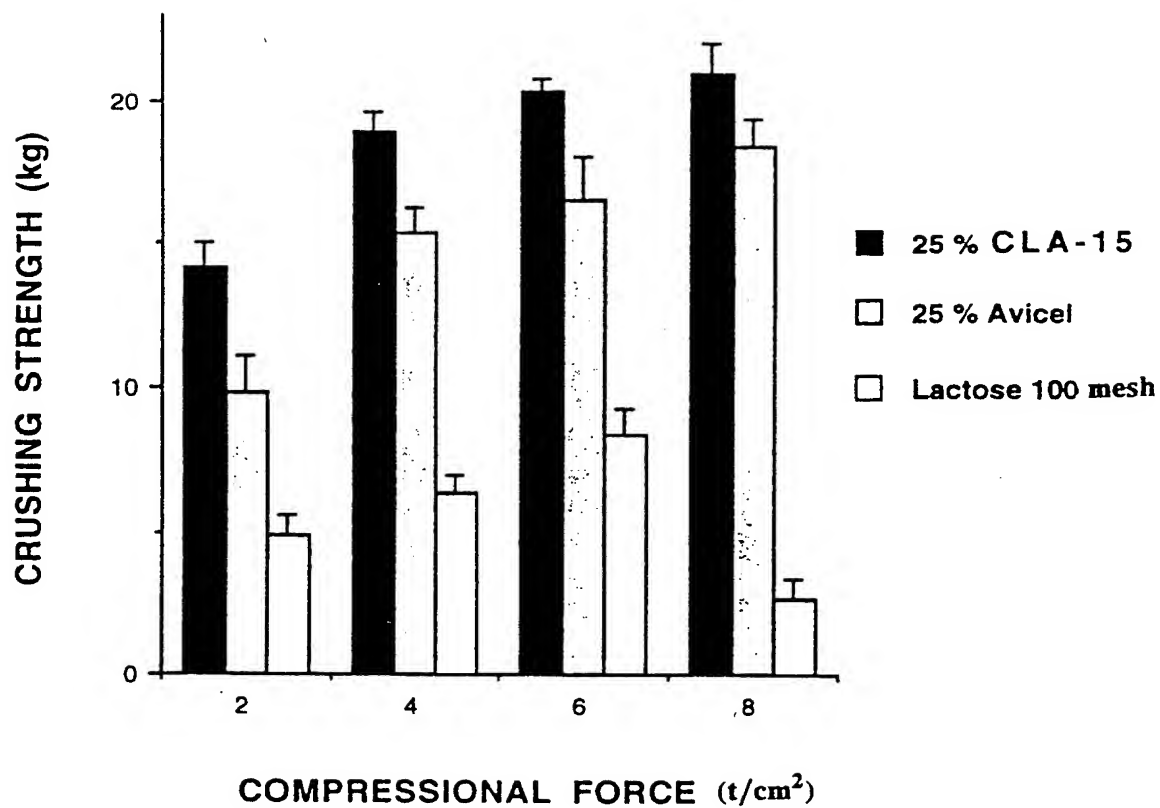
FIGURE 5 . CRUSHING STRENGTH vs CROSS-LINKING DEGREE
(TABLETS COMPRESSED AT A COMPRESSIONAL FORCE OF 8 TONS/cm²
AND CONTAINING VARIOUS PERCENTAGES OF CLA).

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**FIGURE 6 . CRUSHING STRENGTH vs COMPRESSIONAL FORCE
(TABLETS CONTAINING 20% OF CLA-15, 20% OF AVICEL PH-102
OR ONLY α -MONOHYDRATE LACTOSE 100 MESH).**

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**FIGURE 7 . CRUSHING STRENGTH vs COMPRESSIONAL FORCE
(TABLETS CONTAINING 25% OF CLA-15, 25% OF AVICEL PH-102
OR ONLY α -MONOHYDRATE LACTOSE 100 MESH).**

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/CA 94/00163A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 499 648 (NATIONAL STARCH AND CHEMICAL INVESTMENT HOLDING CORPORATION) 26 August 1992 see claims 1-3,5,8-12,14,17-19 see page 3, line 53 - line 56 see page 4, line 4 - line 5 see page 4, line 28 - line 29 see page 4, line 52 - line 55 see page 6, line 49 see page 6, line 53 - line 54 see page 6, line 57 - line 58 see page 7, line 17 - line 20 see example 1 --- -/--	1-10

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Date of the actual completion of the international search

27 May 1994

Date of mailing of the international search report

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Scarponi, U

Int. Patent Application No
PCT/CA 94/00163

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE WPI Week 9233, Derwent Publications Ltd., London, GB; AN 92-269220 (33) see abstract & CA,A,2 041 774 (UNIV. QUEBEC A MONTREAL) 28 May 1992</p> <p style="text-align: center;">---</p>	1-10
Y	<p>PROC. OF THE 19TH INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 1992 pages 30 - 31 V.LENAERTS ET AL. 'CROSSLINKED AMYLOSE TABLETS FOR CONTROLLED-RELEASE OF DRUGS'</p> <p style="text-align: center;">---</p>	1-10
A	<p>US,A,3 622 677 (R.W.P.SHORT) 23 November 1971 cited in the application see the whole document</p> <p style="text-align: center;">-----</p>	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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CA-A-2041774	28-05-92	NONE	
US-A-3622677	23-11-71	NONE	